REMARKS

Request for Interview

Applicants respectfully request a telephonic interview with the Examiner prior to the mailing of the next Office Action in the instant case. If the Examiner has not heard from Applicants' representative before the Examiner is prepared to respond to the instant Amendment, Applicants respectfully ask the Examiner to please contact Applicants below-signed representative to schedule said telephonic interview.

Summary of Office Action

In the Office Action of October 18, 2007, the Examiner indicated that Claims 3 and 11 were objected to due to a typographical error. The Examiner rejected claims 1, 3, 7-8, 9-11, 17-23, 24-30 and 33 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,440,465 to Meisner (hereinafter "Meisner"), in view of U.S. Patent No. 6,358,542 to Cuomo et al. ("hereinafter "Cuomo"), and U.S. Patent Application Publication No. 20030108651 to Crea et al. (hereinafter "Crea"). The Examiner further rejected claims 26-28, 30-31 and 33 under 35 U.S.C. 112, first paragraph, as lacking enablement for the full scope of the claims. The Examiner also indicated that two of the references cited on the information disclosure statement were not published because they did not correspond to published documents. No other issues were raised.

Summary of Amendment

Upon entry of the present Amendment, Claims 3 and 11 will have been amended to correct a minor typo-type error. Claims 1, 3, 5-14, 16-31, 33, and 37-71 remain currently pending, with claims 12-14, 16 and 37-71 being in withdrawn status. By the present Amendment and Remarks, Applicant submits that the rejections have been overcome and respectfully requests reconsideration of the outstanding Office Action.

Applicant's Response

1. Status of Claims

Applicants note that the Examiner has rejected claims 1, 3, 7-8, 9-11, 17-23, 24-30 and 33 under 3 U.S.C. 103(a) (*see*, e.g., Office Action page 3) and has rejected claims 26-28, 30-31 and 33 under 35 U.S.C. 112, first paragraph (*see, e.g.,* Office Action page 6.) However, the Examiner has omitted any reasons for the rejection of claims 5-6 and 31, although the Office Action Summary sheet (PTOL-326) indicates that these claims are in rejected status.

Applicants therefore respectfully request that the Examiner provide the reasons for rejection, if any, of claims 5-6. The Examiner is reminded that any new statement of reasons for the rejection would be considered to be "new grounds" for the rejection, as no basis for the rejection of claims 5-6 has as-yet been provided. The Examiner is therefore precluded from making the next Action *final* on the basis of such grounds. See MPEP 706.07(a).

2. Information Disclosure Statement

The Examiner indicated that the last two documents cited in the IDS of November 14, 2006 were placed in the file but were not considered because they did not comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 in that "they are not a published document" (Office Action page 2.)

Applicants note that 37 CRF 1.98 states that "(a) any information disclosure statement filed under § 1.97 shall include the items listed in paragraphs (a)(1), (a)(2) and (a)(3) of this section [including] (1) A list of all patents, publications, applications, or other information submitted for consideration by the Office." Thus, 37 CFR 1.98 indicates that publications, applications and "other information" may be submitted in an IDS form. Accordingly, the foreign Examination Reports cited in the IDS form are proper and should be considered by the Examiner. Applicants respectfully request that the Examiner indicate consideration of the cited Examination Reports in the next Office Action.

3. Objection to Claims 3 and 11

The Examiner objected to claims 3 and 11 due to a minor typo-type error, namely the presence of an extra period in the claims. This typo-type error is being corrected herewith, and accordingly Applicants respectfully request withdrawal of this objection.

4. Rejection of Claims 1, 3, 7-11, 17-30 and 33 under 35 U.S.C. 103(a) over Meisner, Cuomo and Crea

The Examiner rejected claims 1, 3, 7-11, 17-30 and 33 under 35 U.S.C. 103(a) over Meisner in view of Cuomo and Crea. In particular, the Examiner asserts that Meisner teaches administering oleuropein for the treatment of skin-conditions such as psoriasis, and mentions skin cancer as one of the conditions (*see, e.g.,* Office Action pages 3-4.) The Examiner also asserts that Cuomo teaches administering oleuropein for the treatment of cancer (*see, e.g.,* Office Action page 4) and asserts that Crea teaches different methods of administering oleuropein (*see, e.g.,* Office Action page 4.) This rejection is respectfully traversed.

Claim 1 is not obvious over the combination of Meisner, Cuomo and Crea, because none of the references teach or suggest a method for treating cancer "selected from the group consisting of colon cancer, renal adenocarcinoma and melanoma" by administering a therapeutically effective amount of the compound of the formula as claimed, such as oleuropein.

Meisner teaches compositions for "the treatment of psoriasis and related skin ailments" (Abstract.) The "related skin ailments" taught by Meisner can include other chronic eczematous skin conditions such as atopic dermatitis (*see, e.g.,* column 6, lines 10-15.) Meisner further teaches that such a treatment composition can contain oleuropein, which is believed to have antioxidant properties useful in the treatment of psoriasis (*see, e.g.,* column 4, lines 40-65.)

However, Meisner *does not teach or suggest* the use of oleuropein or other compounds matching the claimed formula for the treatment of any of colon cancer, renal adenocarcinoma and/or melanoma. Instead, in the section to which the Examiner refers, Meisner generally describes conditions related to skin aging, including the thinning of the dermis with age, as well as the increased incidence of skin cancer with aging that is related to skin thinning (*see, e.g.*, column 3, lines 20-45). Meisner compares the incidence of skin cancer and psoriasis as a function of age to speculate on the physiological role of glucosamine (*see, e.g.*, column 4, lines 1-20.) In other words, any description regarding skin cancer on the part of Meisner is intended only for the purposes of describing what is understood about the physiological role of glucosamine, and *is not intended to teach or suggest that oleuropein or any other antioxidant could be used for the treatment of skin cancer*. A mere mention of skin cancer as a skin disorder in the reference does not constitute a teaching of a treatment therefor using the compounds as claimed. In fact, Meisner *teaches against* the method of the instant claims by teaching that psoriasis and skin cancer have *different etiologies*, in that "since psoriasis and atopic dermatitis may strike at a young age, psoriasis is clearly not related to only the thinning skin, in contrast to skin cancer and decreased skin immune response" (column 4, lines 5-10.) Thus, while Meisner teaches providing oleuropein for the treatment of psoriasis, Meisner does not teach or suggest providing oleuropein for the treatment of a cancerous condition such as melanoma.

Cuomo does not make up for the deficiencies of Meisner in that Cuomo does not teach or suggest the treatment of skin cancer or other cancers. In the section to which the Examiner refers, Cuomo teaches that oleuropein is an anti-oxidant found in olive oil (*see, e.g.*, column 2, lines 25-45) and Cuomo further teaches that olive oil is believed to lower the incidence of heart disease and breast cancer (*see, e.g.*, column 1, lines 30-35.) Thus, Cuomo teaches that olive oil may help to *prevent cancer*, and that it is possible that the cancer prevention may be at least in part due to antioxidative effects from oleuropein. However, Cuomo also does not teach or suggest that oleuropein is capable of *treating cancer*, such as skin cancer, as claims. Accordingly, as neither Meisner nor Cuomo teach or suggest *treating cancer* with oleuropein or other compounds of formula I in claim 1, it is considered that the

claimed method is patentable over the references because they fail to teach or suggest each and every limitation of the claim.

It is furthermore noted that one of ordinary skill in the art would understand that a composition that is suitable for the *prevention* of cancer is not necessarily suitable for the *treatment* of the same cancer. For example, while antioxidants may be believed to reduce the incidence of certain types of cancer, the mechanism by which antioxidants work to inhibit cancer occurrence may actually have deleterious effects in the *treatment* of existing cancer. As is known to those of ordinary skill in the art, antioxidants work to promote cell health by reducing the numbers and effects of damaging free radicals in a biological system. However, for a person already having cancerous cells, such cell health promoting compounds could promote the growth and formation of the cancerous cells themselves. In fact, it is common practice for physicians to warn patients prior to chemotherapeutic treatments to not take too many antioxidants, as their use could undesirably promote the health of the cancerous cells it is intended to destroy. It follows therefrom that one of ordinary skill in the art *would not* have found it obvious to provide a compound with antioxidant properties in the *treatment* of a cancerous condition, such as skin cancer/melanoma, because one of ordinary skill in the art would not have expected the antioxidant compounds to be effective in the treatment of the cancer, and would even have expected that administration of the anti-oxidant could have undesirable effects.

In contrast, Applicants have discovered that compounds as claimed are capable of acting via physiological pathways other than just antioxidation to provide actual *treatment* of cancerous conditions, such as skin cancer/melanoma. For example, as described in the instant specification, the compounds as claimed are capable of *treating* various types of cancer by targeting and disrupting the cellular cytoskeleton of the cancer cells, thereby inhibiting the movement and division of the cancer cells (*see, e.g.*, paragraphs [0015]-[0016].) Examples 1-4 of the instant specification give further evidence of the efficacy of the claimed compounds in the treatment of various different types of cancer. This cancer cell targeting and cytoskeleton disrupting activity of the claimed compounds was not known in

the art, and thus the use of such compounds to treat cancer is considered to be patentable over the prior art.

Finally, Crea does not make up for the deficiencies of Meisner and Cuomo. Crea teaches that olive-derived hydroxytyrosol can be used for the treatment of skin damage, such as the protection of skin damage resulting from exposure to ultraviolet radiation (*see, e.g.,* Abstract and paragraph [0083]). In the section to which the Examiner refers, Crea teaches that compositions having the hydroxytyrosol can be formulated in different administration forms, such as parenteral, intravenous, etc. (*see, e.g.,* paragraph [0087]). However, Crea also does not teach or suggest providing the compounds having the formula as claimed for the *treatment of cancer*, such as the treatment of skin cancer/melanoma. It is furthermore noted that as Crea teaches the administration of *hydroxytyrosol*, the teachings therein are not readily combinable with those of Meisner and Cuomo that are directed to the administration of a different compound, namely *oleuropein.*

Accordingly, claim 1 and the claims depending therefrom are patentable over Meisner, Cuomo and Crea because the references do not teach or suggest administering compounds having the formula as claimed for *the treatment of cancer*, such as colon cancer, renal adenocarcinoma and/or melanoma. Applicants thus respectfully request that the rejection under 35 U.S.C. 103(a) of claim 1 and the claims depending therefrom, including claims 9-10 and 17-19, be withdrawn.

Regarding claim 3, it is noted that the claim is similar to claim 1 in that it is directed to the inhibiting the growth, motility, invasiveness and metastasis of cancer cells, the cancer cells being selected from the group consisting of colon cancer, renal adenocarcinoma and melanoma, with a compound having the same formula as in claim 1. Accordingly, claim 3 and the claims depending therefrom are considered to be patentable over the cited references for at least the same reasons as claim 1, and the rejection of claim 3 and claim 10 depending therefrom is respectfully requested to be withdrawn.

Regarding claim 7, it is noted that the claim is similar to claim 1 in that it is directed to *treating cancer*, the cancer being selected from the group consisting of colon cancer, renal adenocarcinoma and melanoma, with a compound that is produced by the hydrolysis of a compound having the same formula as in claim 1. Accordingly, claim 7 and the claims depending therefrom are considered to be patentable over the cited references for at least the same reasons as claim 1, and the rejection of claim 7 and claim 25 depending therefrom is respectfully requested to be withdrawn.

Regarding claim 8, it is noted that the claim is similar to claim 1 in that it is directed to *inhibiting cancer cell growth*, the cancer cells being selected from the group consisting of colon cancer, renal adenocarcinoma and melanoma, with a compound that is produced by the hydrolysis of a compound having the same formula as in claim 1. Accordingly, claim 8 is considered to be patentable over the cited references for at least the same reasons as claim 1, and the rejection of claim 8 is respectfully requested to be withdrawn.

Regarding claim 11, it is noted that the claim is similar to claim 1 in that it is directed to *treating cancer*, the cancer being selected from the group consisting of colon cancer, renal adenocarcinoma and melanoma, with a compound having the same formula as in claim 1. Accordingly, claim 11 and the claims depending therefrom are considered to be patentable over the cited references for at least the same reasons as claim 1, and the rejection of claim 11 and claims 20-24 depending therefrom is respectfully requested to be withdrawn.

Regarding claim 26, it is noted that the claim is similar to claim 1 in that it is directed to *inhibiting cancer cell growth* with a compound produced by the hydrolysis of a compound having the same formula as in claim 1. Accordingly, claim 26 is considered to be patentable over the cited references for at least the same reasons as claim 1, and the rejection of claim 26 is respectfully requested to be withdrawn.

Regarding claim 27, it is noted that the claim is similar to claim 1 in that it is directed to *inhibiting cancer cell growth, motility, invasiveness and metastasis*, with a compound

having a formula that falls within the scope of the formula recited in claim 1. Accordingly, claim 27 and the claims depending therefrom are considered to be patentable over the cited references for at least the same reasons as claim 1, and the rejection of claim 27 and claims 30-31 and 33 depending therefrom is respectfully requested to be withdrawn.

Regarding claim 28, it is noted that the claim is similar to claim 1 in that it is directed to *inhibiting cancer cell growth, motility, invasiveness and metastasis*, with a compound having a formula that falls within the scope of the formula recited in claim 1. Accordingly, claim 28 is considered to be patentable over the cited references for at least the same reasons as claim 1, and the rejection of claim 28 is respectfully requested to be withdrawn.

Regarding claim 29, it is noted that the claim is similar to claim 1 in that it is directed to selectively targeting and delivering an effective amount of a compound to *inhibit the cancerous growth or recurrence of cancer cells*, the cancer cells being selected from the groups consisting of colon cancer, renal adenocarcinoma and melanoma, with a compound having a formula that falls within the scope of the formula recited in claim 1. Accordingly, claim 29 is considered to be patentable over the cited references for at least the same reasons as claim 1, and the rejection of claim 29 is respectfully requested to be withdrawn.

5. Rejection of Claims 26-28, 30-31 and 33 under 35 U.S.C. 112, First Paragraph

The Examiner rejected claims 26-28, 30-31 and 33 under 35 U.S.C. 112, first paragraph, as lacking enablement for the full scope of the claims. In particular, the Examiner asserts that while the specification is enabling for the treatment of specific cancers such as colon cancer, the specification does not reasonably provide enablement for treating a wide variety of cancers (*see, e.g.,* Office Action page 6.) This rejection is respectfully traversed.

Applicants note that the test for whether claims can be considered to be enabled by the specification as originally filed is whether one of ordinary skill in the art would be capable of making and using the invention *without requiring undue experimentation* (MPEP 2164.01, *see, e.g., in re Wands,* 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988)).

Claims 26-28, 30-31 and 33 are directed to methods of treating cancer and/or inhibiting cancer cell growth, motility, etc., by administering one or more of a set of closely related compounds sharing significant common chemical structure, such as oleuropein, which compounds would be understood by those of ordinary skill in the art to have similar physiological treatment effects. With regards to the use of the compounds in the treatment of cancers, in general, it is noted that the specification as originally filed shows that the compounds are capable of acting *via a mechanism that is common to cancer cells* to disrupt the cellular cytoskeleton of the cancer cells and reduce their motility, growth, and invasiveness. Accordingly, as the compounds do not act via a mechanism that is specific to a particular type of cancer cell, but instead operate according to a *general mechanism* applicable to all cancer cells, it is considered that one of ordinary skill in the art would be capable of using the compounds to treat a wide variety of cancers without requiring undue experimentation.

As evidence of the compounds' general action on cancer cells, Applicants respectfully direct the Examiner to Example 4 of the instant specification. This example shows oleuropein's effect on the cellular cytoskeleton of cancer cells by a tube-disruption assay. The oleuropein induces cytoskeletal re-organization that "rounds-up" the cells, thereby disrupting the tubular network. The thus rounded cells don't move and remain in place indefinitely, thereby inhibiting motility of the cells. A comparison of Figures 6A and 6B also shows the difference between untreated cells and cells that have been treated with oleuropein, in terms of the tube collapse by disruption and the rounding of the cells. Examples 1-3 further show the effects of oleuropein on cancer cell invasiveness and cancer cell growth. Accordingly, the specification as originally filed demonstrates that oleuropein and like compounds act to treat cancer by disruption of the cellular cytoskeleton of cancer cells. As the disruption of the cellular cytoskeleton is a mechanism common to cancer cells in general, it is considered that one of ordinary skill in the art would be capable of using the claims compounds to treat a wide variety of cancers without requiring undue experimentation.

It is furthermore noted that Figure 5 shows that anti-cancer activity of oleuropein on five different types of very distinct cancers, namely leukemia, renal cell adenocarcinoma, breast ductal carcinoma, melanoma and colon cancer. These cancers represent a wide variety of different cancer types in that they include both tumor-forming and non-tumor forming cancers, are understood to have differing etiologies and affect different physiological systems, and are treated according to different treatment regimens. For example: leukemia is a cancer of the blood or bone marrow often treated by chemotherapeutic methods; colon cancer typically involves cancerous growths (tumors) in the colon and is treated by surgical methods as well as chemotherapy; breast ductal carcinoma is a neoplasm of the breast ducts; and melanoma is a cancer of the skin attributable to genetic factors and excessive exposure to the sun, which is treated by surgery and if necessary by chemotherapeutic and radiation therapy methods. Regardless of the very different natures of these different cancers, it has been demonstrated by Applicants that oleuropein is nonetheless capable of inhibiting the growth of all of these very distinct types of cancer by disrupting the cellular cytoskeletons of the cancer cells, as is shown in Figure 5. This study thus provides further confirmation of the ability of oleuropein and like compounds to treat cancer, and therefore further enables one of ordinary skill in the art to perform the claimed methods without requiring undue experimentation.

It is furthermore noted that oleuropein, which is a natural compound found in olive oil, and like compounds are known to be highly non-toxic, and thus one of ordinary skill in the art would also understand that the compounds were safe for administration without requiring undue experimentation in that regard.

The Examiner argues that there is no one drug that is capable of treating a wide variety of cancers, and thus performing the methods of the invention would require undue experimentation on the part of those of ordinary skill. Applicants respectfully disagree with this argument, and note that a showing that the compounds can act via a mechanism that is common to all cancers, such as by disrupting the cellular cytoskeleton of the cancer cells, is

considered to be sufficient to show enablement of the claimed methods. To draw an analogy to other medical conditions, since it is known that serotonin re-uptake inhibitors are capable of treating depression, a compound that exhibits this biochemical activity would be understood to have a reasonable expectation of being capable of treating depression, even in the absence of human studies proving their efficacy. Thus, methods using such compounds would be considered to be enabled to those of ordinary skill in the art and not requiring undue experimentation. As another analogy, since anti-bacterial compounds such as penicillin are known to defeat bacterial cells by targeting the bacterial cell wall, a showing of the ability of one or more new compounds to similarly target the bacterial cell wall would also be enabling for the treatment of bacterial infections with such compounds, because it would be understood that a reasonable expectation exists that the new compounds would destroy bacterial cells by the same mechanism as the penicillin. Similarly, as the instantly claimed compounds have been shown to be capable of treating cancers by a general mechanism shared by the cancers, it is considered that one of ordinary skill in the art would be capable of performing the method in its entire scope without requiring undue experimentation.

Accordingly, claims 26-28, 30-31 and 33 are enabled by the originally filed specification for the methods recited therein, and the rejection of these claims under 35 U.S.C. 112, first paragraph, is respectfully requested to be withdrawn.

Conclusion

Applicant respectfully submits that each and every pending claim of the present invention meets the requirements for patentability under 35 U.S.C. §§ 103 and 112, and respectfully requests that the Examiner indicate allowance of each and every pending claim of the present invention.

In view of the foregoing, it is submitted that the Section 103 and 112 rejections have been overcome. Applicant respectfully submits that the amendments to the claims have rendered the Examiner's rejections moot and have placed the claims in a condition for allowance per the Examiner's comments. Accordingly, reconsideration of the outstanding Office Action and allowance of the present application and all the claims therein are respectfully requested and now believed to be appropriate.

If any additional fee is required, please charge Deposit Account Number 19-4330.

Respectfully submitted,

Date: 4/16/08 By: _____

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